General Anesthetics, Local Anesthetics & muscle relaxant

麻醉科 譚炳恒

THE HISTORY OF ANESTHESIA

- Nitrous oxide
  - Horace Wells, dental extraction , 1844.
- Gaseous ether
  - William Morton
  - October 16, 1846
  - Gaseous ether
  - Public demonstration gained world-wide attention
  - Public demonstration consisted of an operating room, “**ether dome,**” where Gilbert Abbot underwent surgery in an unconscious state at the Massachusetts General Hospital
  - no longer used in modern practice, yet considered to be the first “ideal” anesthetic
- Chloroform
  - James Simpson: 1847
- Endotracheal tube discovered in 1878
- Local anesthesia with cocaine in 1885

1846 哈佛大學講堂內的情景

近代麻醉醫學的歷史相當短，起源於美國，1846年美國醫生 Morton 當眾示範以乙醚麻醉病人，從此以後人們發現及合成不少揮發性的氣體，具有麻醉的性質。也由於這些麻醉氣體的出現，近代的手術療法才成為可能。

THE HISTORY OF ANESTHESIA

- Cyclopropane: 1929
  - Most widely used general anesthetic for the next 30 years
- Thiopental in 1934 : Intravenous anesthetic
- Curare first used in 1942
- Halothane: 1956
  - Team effort between the British Research Council and chemists at Imperial Chemical Industries
  - Preferred anesthetic of choice

General Anesthesia
Basic Principles

- Anesthesia defined as the abolition of sensation
- Analgesia defined as the abolition of pain
- Triad of General Anesthesia
  - need for unconsciousness
  - need for analgesia
  - need for muscle relaxation

Requirements for General Anesthesia

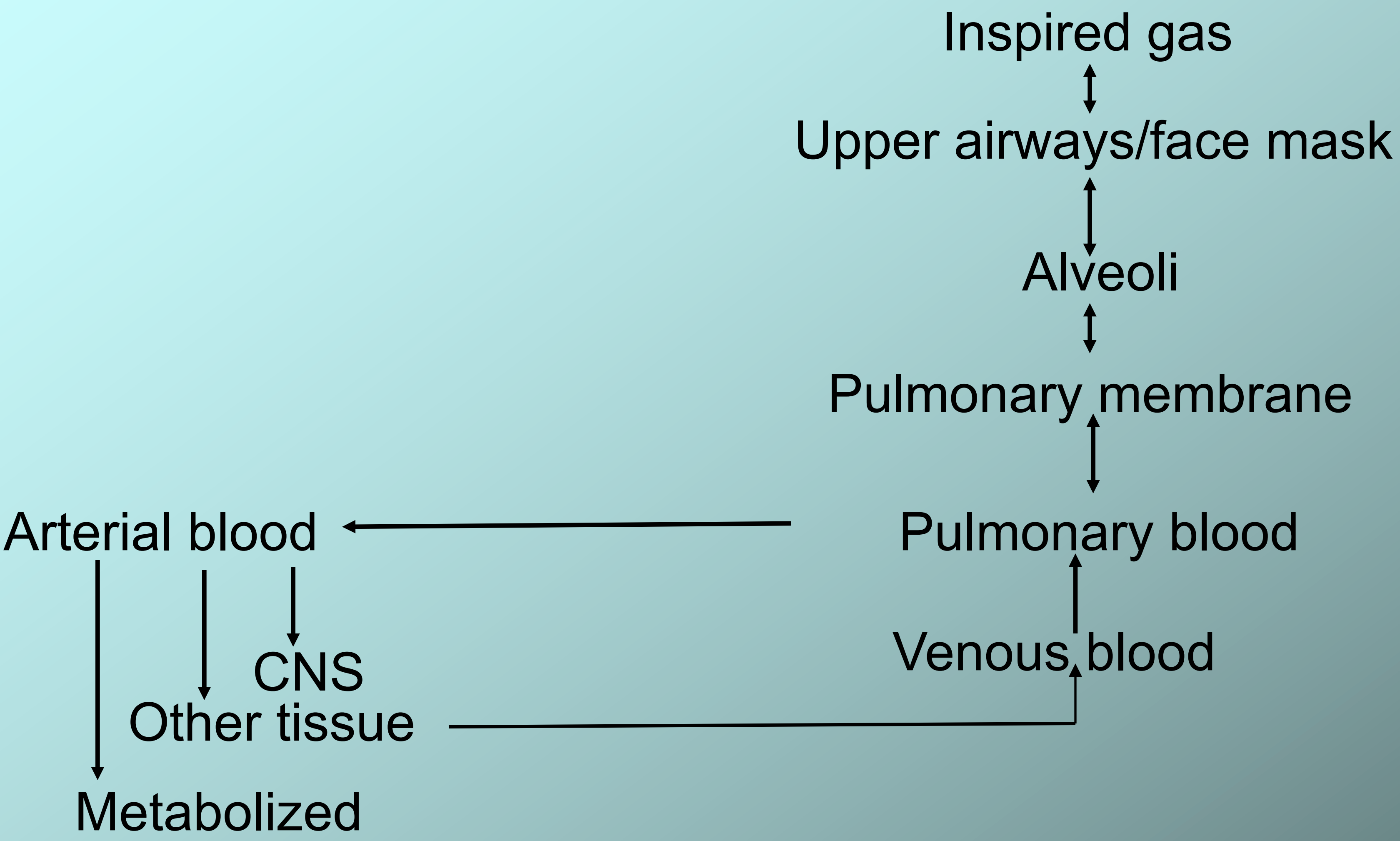
- Premedication
- Induction
  ventilation with or without intubation/ mask
- Maintenance
- Emergence
- Postoperative pain control

Premedication

- Relief of anxiety (benzodiazepine, scopolamine, morphine)
- Reduction of secretions & vagal reflexes (scopolamine, atropine, glycopyrrolate)
  - vagal reflex prominent in children & is provoked by halothane, succinylcholine & stimulation
  - vagal reflex provoked in eye surgery
- Preemptive analgesia
  - Analgesics prior to painful stimuli are more effective than when given afterwards

Anesthesia Machine

Inhalational Agents



Inhalational Anesthetic Agents

- The delivery of gases or vapors from the respiratory system to produce anesthesia
- Pharmacokinetics--uptake, distribution, and elimination from the body
- **Minimum alveolar concentration** or **MAC**
  - concept used to compare the strengths, or potency, of anaesthetic vapoursin simple terms
  - defined as the concentration of the vapour in the lungs that is needed to prevent movement (motor response) in 50% of subjects in response to surgical (pain) stimulus.

Inhalational Agents

GAS

- Nitrous oxide

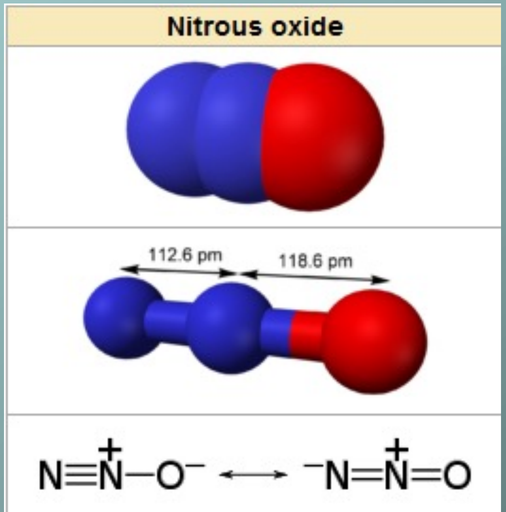
VOLATILE AGENTS

- Halothane
- Enflurane
- Isoflurane
- Sevoflurane
- Desflurane

Nitrous Oxide

Nitrous Oxide

- Colorless, odorless, tasteless, and does not burn
- Simple linear compound
- Only anesthetic agent that is inorganic
- Not metabolized



Nitrous Oxide

- MAC : 105%
- Low potency
- Low blood solubility (quick recovery)
- Weak anesthetic, powerful analgesic
- Needs other agents for surgical anesthesia

Nitrous Oxide
Systemic effect

- Minimal effects on heart rate and blood pressure
- May cause myocardial depression in sick patients
- Little effect on respiration
- Safe, efficacious agent

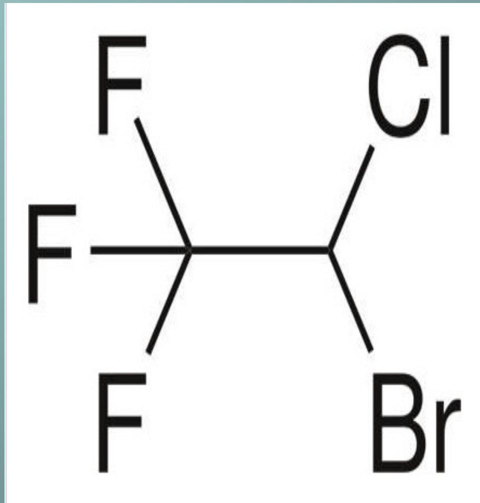
Nitrous Oxide
Side effects

- Impurities toxic
- Hypoxic mixtures can be used
- Inhibits methionine synthetase (precursor to DNA synthesis)
- Inhibits vitamin B-12 metabolism
- Dentists, OR personnel, abusers at risk
- Diffusion into closed spaces

Halothane

Halothane

- Most potent inhalational anesthetic
- MAC of 0.75%
- Efficacious in depressing consciousness
- Very soluble in blood and adipose
- Prolonged emergence
- Halogen substituted ethane
- Volatile liquid easily vaporized, stable, and nonflammable



Halothane Systemic Effects

- Inhibits sympathetic response to painful stimuli
- Inhibits sympathetic driven baroreflex response (hypovolemia)
- Sensitizes myocardium to effects of exogenous catecholamines-- ventricular arrhythmias
  - Johnson found median effective dose 2.1 ug/kg
  - Limit of 100 ug or 10 mL over 10 minutes
  - Limit dose to 300 ug over one hour
  - Other medications

Halothane Systemic Effects

- Decreases respiratory drive
  - central response to CO_2 and peripheral to O_2
  - Respirations shallow-- atelectasis
  - Depresses protective airway reflexes
- Depresses myocardium
  - lowers BP and slows conduction
  - Mild peripheral vasodilation

Halothane Side Effects

- Halothane Hepatitis
  - 1/10,000
  - fever, jaundice, hepatic necrosis, death
  - metabolic breakdown products are hapten-protein conjugates
  - immunologically mediated assault
  - exposure dependent

Halothane Side Effects

- Malignant Hyperthermia
  - 1/60,000 with succinylcholine to 1/260,000 without
  - Halothane in 60%, succinylcholine in 77%
  - Rapid rise in body temperature
  - Muscle rigidity, most common masseter rigidity
  - Tachycardia
  - Rhabdomyolysis
  - Acidosis
  - Hyperkalemia
  - Family history

Halothane Side Effects

- Malignant Hyperthermia
- Treatment
  - early detection, d/c agents, hyperventilate, bicarb, IV dantrolene (2.5 mg/kg), ice packs/cooling blankets, lasix/mannitol/fluids. ICU monitoring
  - Susceptible patients-- preop with IV dantrolene, keep away inhalational agents and succinylcholine

Isoflurane

Isoflurane

- Synthesized in 1965 by Terrell, introduced into practice in 1984
- MAC : 1.30 %
- Not carcinogenic
- Nonflammable,pungent
- Less soluble than halothane or enflurane

Isoflurane Systemic Effects

- Depresses respiratory drive and ventilatory responses
- Myocardial depressant
- Inhibits sympathetic baroreflex response
- Sensitizes myocardium to catecholamines

Isoflurane
Systemic Effects

- Produces most significant reduction in systemic vascular resistance
- Coronary steal syndrome
- Increased ICP
- Excellent muscle relaxant-- potentiates effects of neuromuscular blockers

Isoflurane
Side Effects

- Bronchoirritating, laryngospasm
- Little metabolism (0.2%) -- low potential of organotoxic metabolites
- No EEG activity like enflurane

Sevoflurane

Sevoflurane

- Nonflammable fluorinated isopropyl ether
- MAC 2.0
- Low solubility in blood
  - rapid induction and emergence
- Minimal systemic effects
  - mild respiratory and cardiac suppressi
- Few side effects
- Expensive

Sevoflurane

- Sevoflurane reacts with CO_2 absorbents to form a special haloalkene, the so-called Compound A.
- Kidney damage.
- The minimum fresh gas flow has been recommended to be at least 2 liters per minute.
- Dose-dependent decrease in arterial blood pressure due to peripheral vasodilatation.

Sevoflurane

- Not sensitize the heart to arrhythmias or cause coronary artery steal syndrome.
- Not irritate the airway.
- Mask induction in pediatric patients.
- Like all other inhalation anesthetics, can trigger malignant hyperthermia

Desflurane

Desflurane

- Fluorinated methyl ethyl ether
- Nonflammable
- MAC 6.0
- Desflurane is very resistant to degradation by soda lime and can therefore be used during low flow or closed system anesthesia.

Desflurane

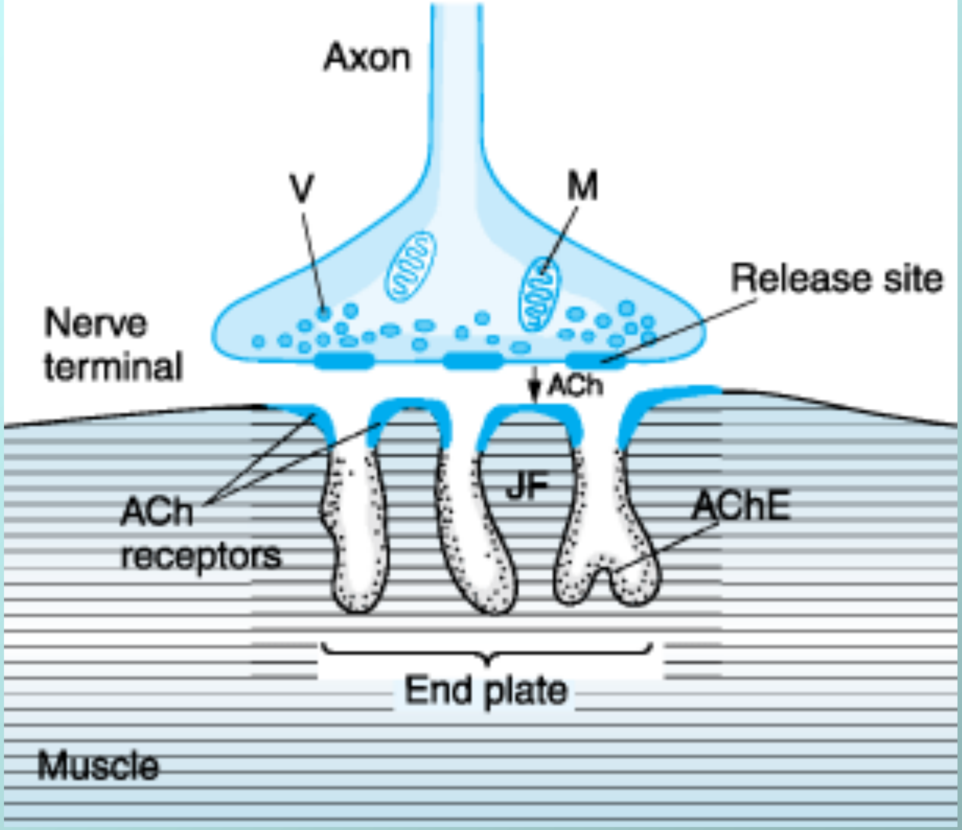
- MAC 6
- Desflurane may cause coughing and excitation during induction
- Therefore not be used without intravenous anesthetics.
- Low tissue solubility results in rapid elimination and awakening.

Muscle relaxants

History

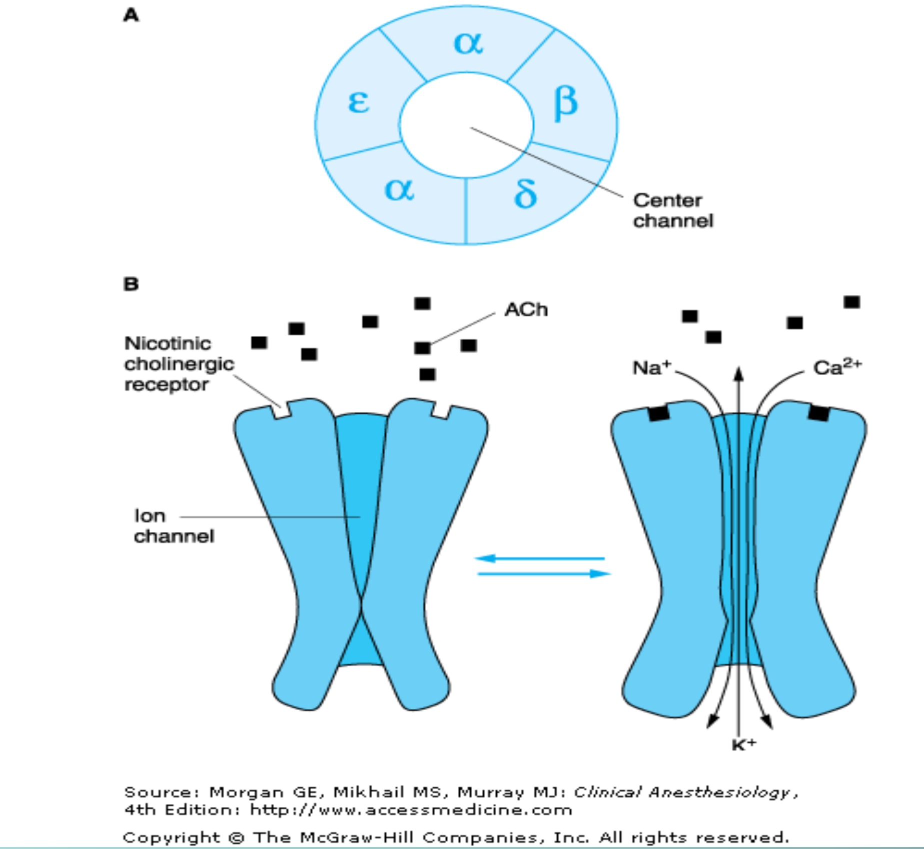
- Due to inhalational and intravenous agents do not fully provide control of muscle tone
- In 1942, Harold Griffith published the results of a study using a refined extract of curare (a South American arrow poison) during anesthesia.
- It is important to realize that neuromuscular junction blocking agents produce paralysis, not anesthesia.
- In other words, muscle relaxation does not ensure unconsciousness, amnesia, or analgesia.

Neutomuscular Transmission



The neuromuscular junction.
V, transmitter vesicle; M, mitochondrion; ACh, acetylcholine; AChE, acetylcholinesterase; JF, junctional folds.

ACh receptor



A: 2 α subunits that actually bind ACh and the center channel.
B: Binding of ACh to receptors on muscle end-plate causes channel opening and ion flux.

The sodium channel

- The sodium channel is a transmembrane protein that has two functional gates.
- Sodium ions pass only when both gates are open.
- Opening of the lower (inactivation) gate is time dependent, whereas the upper gate is voltage dependent.

The sodium channel

- The channel therefore possesses 3 functional states.
  - At rest the lower gate is open but the upper gate is closed (A).
  - When the muscle membrane reaches threshold voltage depolarization, the upper gate opens and sodium can pass (B).
  - Shortly after the upper gate opens the time-dependent lower gate closes (C).

- When the membrane repolarizes to its resting voltage the upper gate closes and the lower gate opens (A).

Schematic sodium channel

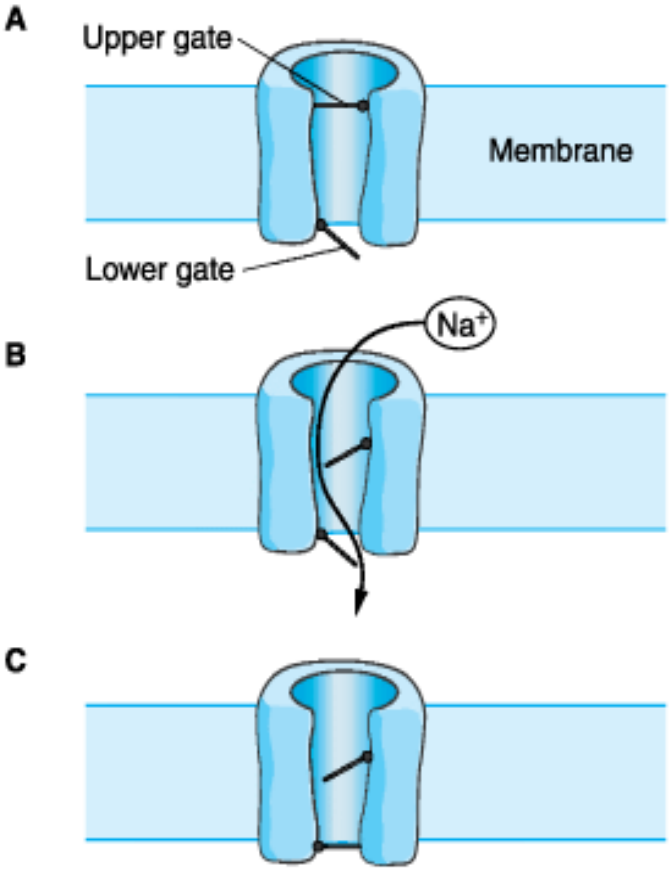


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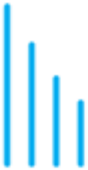
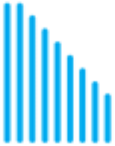
Table 9–2. Evoked Responses during Depolarizing (Phase I and Phase II) and Nondepolarizing Block.

	Depolarizing Block		
Normal Evoked Stimulus	Phase I	Phase II	Nondepolarizing Block
Train-of-four	Constant but diminished	Fade 	Fade
Tetany	Constant but diminished	Fade 	Fade
Double-burst stimulation ($DBS_{3,2}$)	Constant but diminished	Fade	Fade
Posttetanic potentiation	Absent	Present	Present

Muscle Relaxants

1. Depolarzing
2. Nodepolarizing

Mechanism_1
Depolarizing muscle relaxants

- Similar to ACh, all neuromuscular blocking agents are quaternary ammonium compounds affinity to **nicotinic ACh receptors**.
- Depolarizing muscle relaxants very closely resemble ACh and therefore readily bind to ACh receptors, generating a muscle action potential.
- Unlike ACh, however, these drugs are ***not*** metabolized by acetylcholinesterase, and their concentration in the synaptic cleft does not fall as rapidly, resulting in a prolonged depolarization
- Continuous end-plate depolarization causes muscle relaxation because opening of the lower gate in the sodium channels is time limited

Mechanism_2
Depolarizing muscle relaxants

- After the initial excitation and opening , these sodium channels close and cannot reopen until the end-plate repolarizes.
- The end-plate cannot repolarize as long as the depolarizing muscle relaxant continues to bind to ACh receptors; this is called a phase I block.
- After a period of time, prolonged end-plate depolarization can cause ionic and conformational changes in the ACh receptor that result in a phase II block, which clinically resembles that of nondepolarizing muscle relaxants

Mechanism
Nondepolarizing muscle relaxants

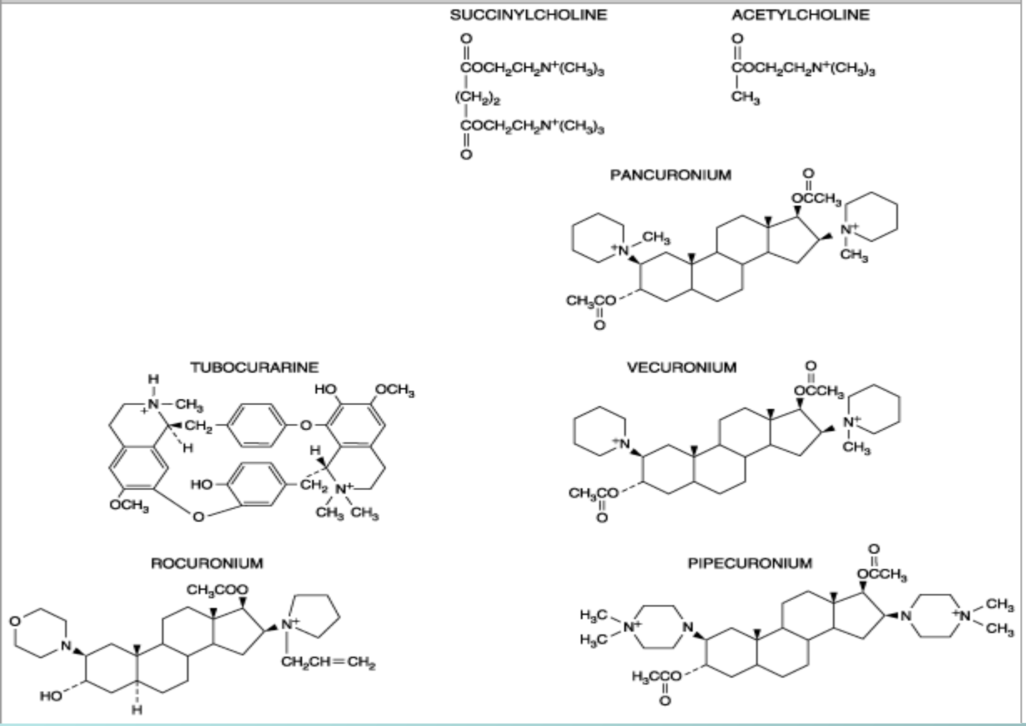
- Nondepolarizing muscle relaxants bind ACh receptors but are incapable of inducing the conformational change necessary for ion channel opening.
- Because ACh is prevented from binding to its receptors, no end-plate potential develops
- Depolarizing muscle relaxants act as ACh receptor agonists
- Nondepolarizing muscle relaxants as competitive antagonists

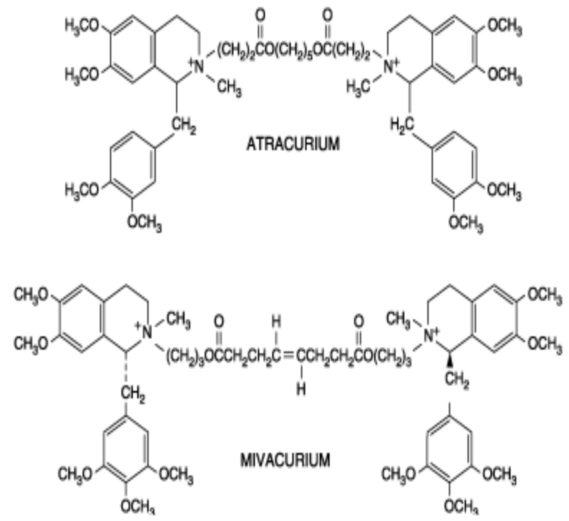
Table 9–1. Depolarizing and Nondepolarizing Muscle Relaxants.

Depolarizing	**Nondepolarizing**
Short-acting	Short-acting
Succinylcholine	Mivacurium
	Intermediate-acting
	Atracurium
	Cisatracurium
	Vecuronium
	Rocuronium
	Long-acting
	Doxacurium
	Pancuronium
	Pipecuronium

Chemical structure

Figure 9–4.





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Chemical structures of neuromuscular blocking agents.

Muscle relaxants dose

Drug	ED_{95} for Adductor Pollicis During N_2/O_2 Anesthesia (mg/kg)	Intubation Dose (mg/kg)	Onset of Action for Intubating Dose (min)	Duration of Intubating Dose (min)	Maintenance Dosing by Boluses (mg/kg)	Maintenance Dosing by Infusion (μg/kg/min)
Succinylcholine	0.5	1.0	0.5	5–10	0.15	2–15 mg/min
Rocuronium	0.3	0.8	1.5	35–75	0.15	9–12
Mivacurium	0.08	0.2	2.5–3.0	15–20	0.05	4–15
Atracurium	0.2	0.5	2.5–3.0	30–45	0.1	5–12
Cisatracurium	0.05	0.2	2.0–3.0	40–75	0.02	1–2
Vecuronium	0.05	0.12	2.0–3.0	45–90	0.01	1–2
Pancuronium	0.07	0.12	2.0–3.0	60–120	0.01	–
Pipecuronium	0.05	0.1	2.0–3.0	80–120	0.01	–
Doxacurium	0.025	0.07	4.0–5.0	90–150	0.05	–

Table 9–8. Diseases with Altered Responses to Muscle Relaxants.

Disease	Response to Depolarizers	Response to Nondepolarizers
Amyotrophic lateral sclerosis	Contracture	Hypersensitivity
Autoimmune disorders (systemic lupus erythematosus, polymyositis, dermatomyositis)	Hypersensitivity	Hypersensitivity
Burn injury	Hyperkalemia	Resistance
Cerebral palsy	Slight hypersensitivity	Resistance
Familial periodic paralysis (hyperkalemic)	Myotonia and hyperkalemia	Hypersensitivity?
Guillain–Barré syndrome	Hyperkalemia	Hypersensitivity
Hemiplegia	Hyperkalemia	Resistance on affected side
Muscular denervation (peripheral nerve injury)	Hyperkalemia and contracture	Normal response or resistance
Muscular dystrophy (Duchenne type)	Hyperkalemia and malignant hyperthemia	Hypersensitivity
Myasthenia gravis	Resistance and proneness to phase II block	Hypersensitivity
Myasthenic syndrome	Hypersensitivity	Hypersensitivity
Myotonia (dystrophica, congenita, paramyotonia)	Generalized muscular contractions	Normal or hypersensitivity
Severe chronic infection (tetanus, botulism)	Hyperkalemia	Resistance

Liver or kidney disease

- As a general rule, the more potent the nondepolarizing muscle relaxant the longer its speed of onset.
- Doxacurium, pancuronium, vecuronium, and pipecuronium are partially excreted by the kidneys, and their action is prolonged in patients with renal failure.
- Cirrhotic liver disease and chronic renal failure often result in an increased volume of distribution and a lower plasma concentration for a given dose of water-soluble drugs, such as muscle relaxants.

Liver or kidney disease

- On the other hand, drugs dependent on hepatic or renal excretion may demonstrate prolonged clearance.
- Thus, depending on the drug, a greater initial dose—but smaller maintenance doses—might be required in these diseases.
- Atracurium and cisatracurium undergo degradation in plasma at physiological pH and temperature by organ-independent Hofmann elimination.

Nondepolarizing Muscle Relaxants

- Competitively inhibit end plate nicotinic cholinergic receptor
- Intermediate acting (15-60 minutes): atracurium, cisatracurium, vecuronium, mivacurium, rocuronium
- Long acting (over 60 minutes): pancuronium, tubocurarine, metocurine

Nondepolarizing Muscle Relaxants

- Tubocurare-- suppress sympathetics, mast cell degranulation
- Pancuronium-- blocks muscarinics
- Reversal by anticholinesterase-- inhibit acetylcholinesterase
  - **neostigmine**, pyridostigmine, edrophonium
  - side effects muscarinic stimulation

Nondepolarizing Muscle Relaxants
Pancuronium

- Hypertension and tachycardia may occur in patients given pancuronium.
- These cardiovascular effects are caused by the combination of vagal blockade and catecholamine release from adrenergic nerve endings.

Nondepolarizing Muscle Relaxants
Rocuronium

- Rocuronium (0.9–1.2 mg/kg) has an onset of action that approaches succinylcholine (60–90 s), making it a suitable alternative for rapid-sequence inductions, but at the cost of a much longer duration of action.

Table 9–6. A Summary of the Pharmacology of Nondepolarizing Muscle Relaxants

Relaxant	Chemical Structure1	Metabolism	Primary Excretion	Onset2	Duration3	Histamine Release4	Vagal Blockade5
Atracurium	B	+++	Insignificant	++	++	+	0
Cisatracurium	B	+++	Insignificant	++	++	0	0
Mivacurium	B	+++	Insignificant	++	+	+	0
Doxacurium	B	Insignificant	Renal	+	+++	0	0
Pancuronium	S	+	Renal	++	+++	0	++
Pipecuronium	S	+	Renal	++	+++	0	0
Vecuronium	S	+	Biliary	++	++	0	0
Rocuronium	S	Insignificant	Biliary	+++	++	0	+

[1]B, benzylisoquinolone; S, steroidal.

[2]Onset: +, slow; ++, moderately rapid; +++, rapid.

[3]Duration: +, short; ++, intermediate; +++, long.

[4]Histamine release: 0, no effect; +, slight effect; ++, moderate effect; +++, marked effect.

[5]Vagal blockade: 0, no effect; +, slight effect; ++, moderate effect.

Depolarizing Muscle Relaxant

Succinylcholine

- Depolarizing muscle relaxants
- Consists of two joined ACh molecules
- Acetylcholine (ACh) receptor agonists
  - Fasciculation
  - Rapid onset: 60 sec
  - Short duration: 5min
- Metabolism
  - Not metabolized by acetylcholinesterase
  - Diffuse away from NM junction
  - Hydrolyzed in the plasma and liver pseudocholinesterase

Succinylcholine

- 1.5 to 2.0 mg/kg , 60 seconds IV
- 4 mg/kg, IM
- Absolute contraindication
  - muscular dystrophy, recent burn injury, spinal cord transaction, and/or immobilization,family history of malignant hyperthermia, hyperkalemia
- Relative contraindication: all children by the FDA

Succinylcholine contraindication

- succinylcholine-induced depolarization to raise serum potassium by 0.5 mEq/L.
- Succinylcholine is considered contraindicated
  - In the routine management of children and adolescent
  - Risk of hyperkalemia, rhabdomyolysis, and cardiac arrest in children with undiagnosed myopathies.
  - Burn injury, massive trauma, neurological disorders

Table 9–5. Conditions Causing Susceptibility to Succinylcholine-Induced Hyperkalemia.
Burn injury
Massive trauma
Severe intraabdominal infection
Spinal cord injury
Encephalitis
Stroke
Guillain-Barré syndrome
Severe Parkinson's disease
Tetanus
Prolonged total body immobilization
Ruptured cerebral aneurysm
Polyneuropathy
Closed head injury
Hemorrhagic shock with metabolic acidosis
Myopathies (eg, Duchenne's dystrophy)

Reversal

- Redistribution,
- Gradual metabolism,
- Excretion of the relaxant by the body,
- Reversal agents (eg, cholinesterase inhibitors) that inhibit acetylcholinesterase enzyme activity.

Reversal Agents

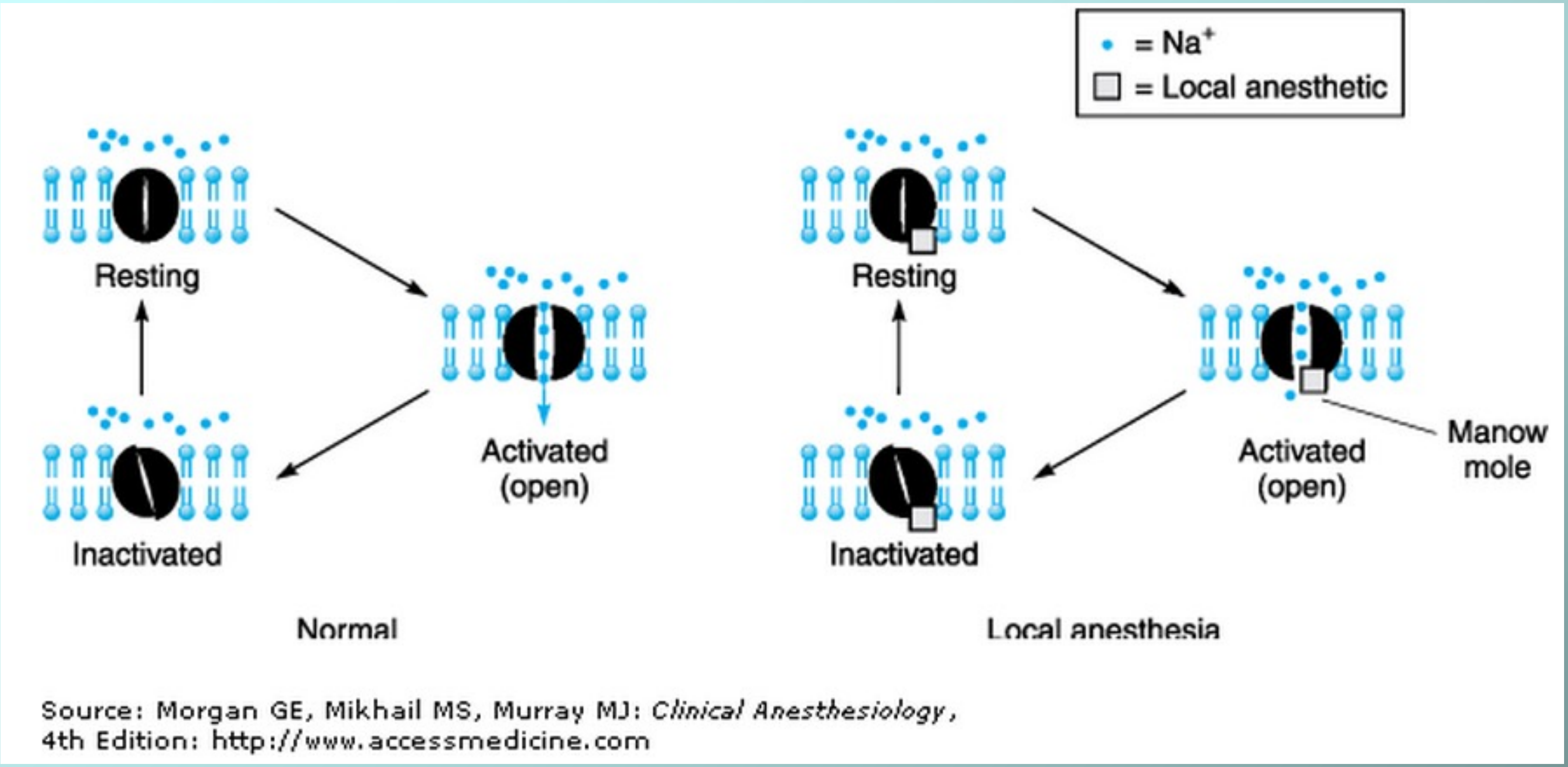
- Neostigmine 0.05 mg/kg + Atropine 0.015 mg/kg
- Adequate strength ventilation
  - Spontaneous breath
  - Regular and adequate volume
  - Ability to flex hips for children

Local anesthetics

History
Local Anesthetics

- Followed general anesthesia by 40 years
- Koller used cocaine for the eye in 1884
- Halsted used cocaine as nerve block
- First synthetic local-- procaine in 1905
- Lidocaine synthesized in 1943

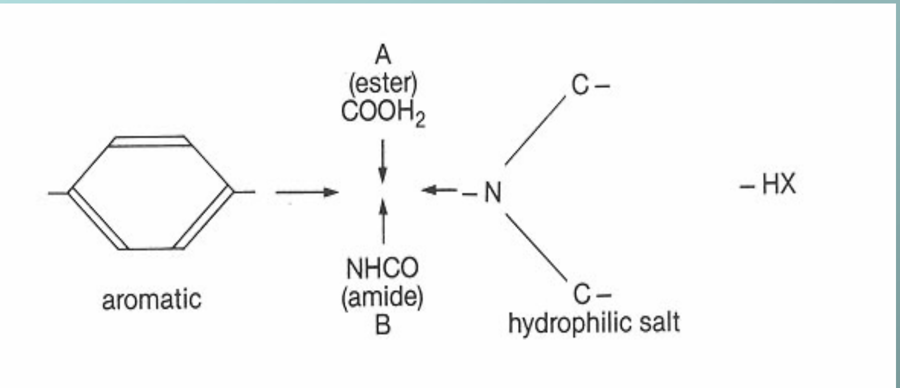
Mechanism
block sodium channel



- Voltage-gated sodium channels exist in three states—resting, activated (open), and inactivated.
- Local anesthetic binds and blocks the voltage-gated sodium channel from inside the cell, interfering with the large transient sodium influx associated with membrane depolarization.

Local Anesthetics

- Linear molecules that have a lipophilic and hydrophilic end (ionizable)
  - low pH-- more in ionized state and unable to cross membrane
  - adding sodium bicarb-- more in non-ionized state



Two groups

- Esters
  - esters metabolized by plasma cholinesterase
- Amides
  - amides metabolized by cytochrome **p-450**

Table 14–2. Physicochemical Properties of Local Anesthetics.

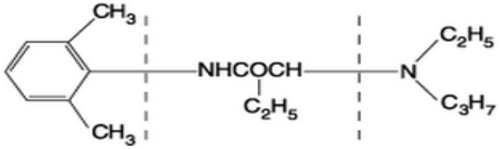
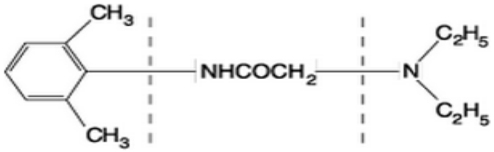
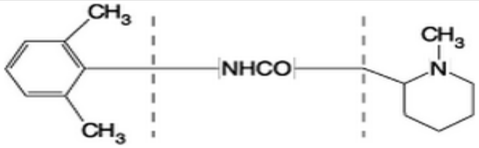
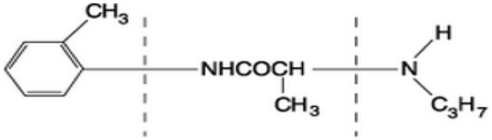
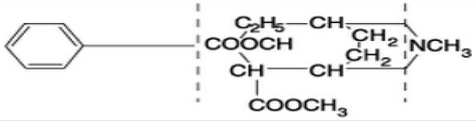
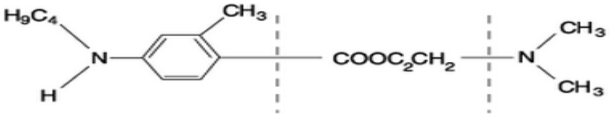
Generic (Proprietary)	Ring	Structure Chain	Amine	Potency and Lipid Solubility	pK_a	Duration and Protein Binding
Amides						
Bupivacaine (Marcaine) and levobupivacaine				++++	8.1	++++
Etidocaine (Duranest)				++++	7.7	++++
Lidocaine (Xylocaine)				++	7.8	++
Mepivacaine (Carbocaine)				++	7.6	++
Prilocaine (Citanest)				++	7.8	++
Esters						
Chloroprocaine (Nesacaine)[1]				+	9.0	+
Cocaine				++	8.7	++
Procaine				+	8.9	+
Tetracaine (Pontocaine)				++++	8.2	+++

Table 14–3. Clinical Use of Local Anesthetic Agents.

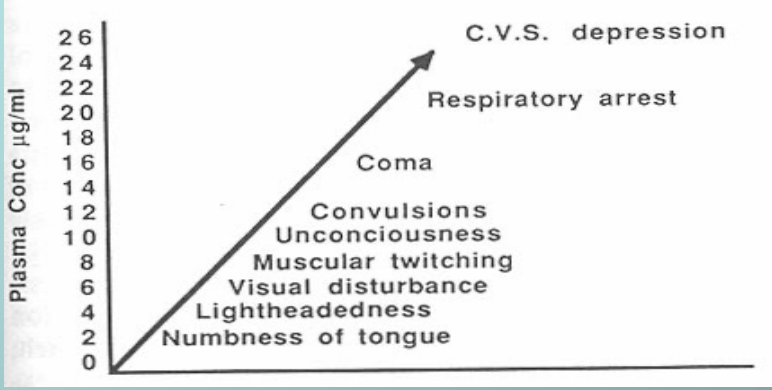
Agent	Techniques	Concentrations Available	Maximum Dose (mg/kg)	Typical Duration of Neural Blockade[1] (h)
Esters				
Benzocaine	Topical	20%	NA[2]	0.5–1
Chloroprocaine	Epidural, infiltration, peripheral nerve block	1%, 2%, 3%	12	0.5–1
Cocaine	Topical	4%, 10%	3	0.5–1
Procaine	Spinal, infiltration, peripheral nerve block	1%, 2%, 10%	12	0.5–1
Tetracaine (amethocaine)	Spinal, topical	0.2%, 0.3%, 0.5%, 1%, 2%	3	1.5–6
Amides				
Bupivacaine	Epidural, spinal, infiltration, peripheral nerve block	0.25%, 0.5%, 0.75%	3	1.5–8
Lidocaine (lignocaine)	Epidural, spinal infiltration, peripheral nerve block, intravenous regional, topical	0.5%, 1%, 1.5%, 2%, 4%, 5%	4.5	0.75–2
			7 (with epinephrine)	
Mepivacaine	Epidural, infiltration, peripheral nerve block	1%, 1.5%, 2%, 3%	4.5	1–2
			7 (with epinephrine)	
Prilocaine	Peripheral nerve block (dental)	4%	8	0.5–1
Ropivacaine	Epidural, spinal, infiltration, peripheral nerve block	0.2%, 0.5%, 0.75%, 1%	3	1.5–8

Potency

- Lipid solubility
- Penetrate membranes
- Cm
  - Minimum concentration of local anesthetic that will block nerve impulse conduction

Local Anesthetic Toxicity

- Central nervous system
- particularly vulnerable
- premonitory signs of overdose in awake patients
  - initially-- lightheadedness, circumoral numbness, dizziness, tinnitus, visual change
  - later-- drowsiness, disorientation, slurred speech, loss of consciousness, convulsions
  - finally-- respiratory depression



Local Anesthetic Toxicity

- Cardiovascular
  - myocardial depression and vasodilation--hypotension and circulatory collapse
- Allergic reactions-- rare (less than 1%)
  - Preservatives
  - metabolites of esters

    derivatives of *p*-aminobenzoic acid, a known allergen
  - rash, bronchospasm

Prevention of Toxicity

- Primarily from intravascular injection or excessive dose -- anticipation
  - Aspirate before injection
  - Slow injection
  - Ask about CNS toxicity
  - Have monitoring available
  - Prepare with resuscitative equipment, CNS-depressant drugs, cardiovascular drugs

Treatment of Toxicity

- All cases:
  - Assure adequate airway and ventilation
  - Administer supplemental oxygen
- Seizures:
  - Thiopental, Midazolam, or Porpofol
- Hypotension
  - Trendelenburg position (head down, legs up)
  - IV fluid bolus
  - Vasopressors
- Dysrhythmias:
  - ACLS
  - Bupivacaine cardiac toxicity, IV lipid or cardiopulmonary bypass

Cocaine

- South American Indians used to induce euphoria, reduce hunger, and increase work tolerance in sixth century
- Vasoconstriction when applied topically
- Safe limits (200-400 mg)-- use with epinephrine clinically

Cocaine

- Inhibits norepinephrine reuptake
- Potentiating adrenergic stimulation.
- Hypertension and ventricular ectopy.
- Contraindicates in halothane

Lidocaine

- 1.5 mg/kg may be effective
  - Block the reflex bronchoconstriction sometimes associated with intubation
  - Some types of ventricular arrhythmias

- Neurotoxicity in intrathecal injection lidocaine = tetracaine > bupivacaine > ropi vacaine

Bupivacaine

- Unintentional intravascular injection
  - severe cardiotoxic reactions
  - Hypotension
  - atrioventricular heart block
  - idioventricular rhythms
  - life-threatening arrhythmias such as ventricular tachycardia and fibrillation.
- Risk factors:
  - Pregnancy, young children, hypoxemia, and respiratory acidosis are predisposing risk factors

Thanks for your attention!!